CLAIMS

1. An isolated nucleic acid molecule encoding a TIE-2 ligand.

2. An isolated nucleic acid molecule according to claim 1 wherein the nucleic acid sequence is:

(a) the nucleic acid sequence comprising the coding region of the human TIE-2 ligand as set forth in Figure 4 or Figure 5;

(b) a nucleic acid sequence that hybridizes under moderately stringent conditions to the nucleic acid sequence of (a) and which encodes a TIE-2 ligand that binds TIE-2 receptor; or

(c) a nucleic acid sequence which, but for the degeneracy of the genetic code would hybridize to a nucleic acid sequence of (a) or (b), and which encodes a TIE-2 ligand that binds TIE-2 receptor.

3. An isolated nucleic acid molecule according to claim 2 wherein the encoded TIE-2 ligand is a TIE-2 agonist.

4. An isolated nucleic acid molecule according to claim 1 wherein the nucleic acid sequence is

(a) the nucleic acid sequence comprising the coding region of the human TIE-2 ligand as set forth in Figure 6;

(b) the nucleic acid sequence comprising the coding region of the fibrinogen-like domain of the human TIE-2 ligand as set forth in Figure 4, 5 or 6;

(c) a nucleic acid sequence that hybridizes under moderately stringent conditions to the nucleic acid sequence of (a) and which encodes a TIE-2 ligand that binds TIE-2 receptor; or

(d) a nucleic acid sequence which, but for the degeneracy of the genetic code would hybridize to a nucleic acid sequence of (a) or (b), and which encodes a TIE-2 ligand that binds TIE-2 receptor

5. An isolated nucleic acid molecule according to claim 4 wherein the encoded TIE-2 ligand is a TIE-2 antagonist.

6. A vector which comprises a nucleic acid molecule of any one of the preceding claims.

7. A vector according to claim 6 wherein the nucleic acid molecule is operatively linked to an expression control sequence capable of directing its expression in a host cell.

8. A vector according to claim 6 or 7 which is a plasmid.

9. A plasmid according to claim 8 designated pJFE14 encoding TIE-2 ligand (ATCC Accession No. 75910).

10. A plasmid according to claim 8 designated pBluescript KS encoding human TIE-2 ligand 2 (ATCC Accession No. 75963).

11. A vector according to claim 6 or 7 designated as λgtlO encoding hTIE2 ligand 1 (ATCC Accession No. 75928).

12. An isolated TIE-2 ligand substantially free of other proteins.

13. An isolated TIE-2 ligand according to claim 12 encoded by a nucleic acid molecule according to claim 1.

14. An isolated TIE-2 ligand according to claim 12 encoded by a nucleic acid according to claim 2 or 3.

15. An isolated TIE-2 ligand according to claim 12 encoded by a nucleic acid according to claim 4 or 5.

16. A host-vector system for the production of a ligand according to any one of claims 12 to 15 which comprises a vector according to any one of claims 6 to 11 in a host cell.

17. A host-vector system according to claim 16 wherein the host cell is a bacterial, yeast, insect or mammalian cell.

18. A host vector system comprising the host vector system of claim 16 or 17 and a nucleic acid encoding the TIE-2 receptor.

19. A method of producing a ligand as defined in any one of claims 12 to 15 which comprises growing cells of a host-vector system according to any one of claims 16 to 18 under conditions permitting production of the ligand, and recovering the ligand so produced.

20. An antibody which specifically binds the ligand of any one of claims 12 to 15.

21. An antibody according to claim 20 which is a monoclonal antibody.

22. A receptorbody which specifically binds the ligand of any one of claims 12 to 15.

23. An isolated nucleic acid molecule encoding a receptorbody according to claim 22.

24. A vector comprising a nucleic acid molecule according to claim 23.

25. A vector according to claim 24 which is a plasmid.

26. A plasmid according to claim 25 designated vTIE-2 receptorbody (ATCC Deposit VR2484).

27. A conjugate comprising a ligand according to any one of claims 12 to 15 and, conjugated thereto, a cytotoxic agent.

28. A conjugate according to claim 27 wherein the cytotoxic agent is a radioisotope or toxin.

29. A pharmaceutical composition comprising a TIE-2 ligand according to any one of claims 12 to 15 and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising an antibody according to claim 20 or 21 and a pharmaceutically acceptable carrier.

31. A pharmaceutical composition comprising a receptorbody according to claim 22 and a pharmaceutically acceptable carrier.

32. A pharmaceutical composition comprising a conjugate according to claim 27 or 29 and a pharmaceutically acceptable carrier.

33. A ligand according to any one of claims 12 to 15, an antibody according to claim 20 or 21, a receptorbody according to claim 22, a conjugate according to claim 27 or 29, or a composition according to any one of claims 29 to 32 for use in a method of treatment of the human or animal body, or in a method of diagnosis.

34. A ligand according to claim 14 for use in a method of treatment of the human or animal body.

35. A ligand according to claim 15 for use in a method of treatment of the human or animal body.

36. An antibody or receptorbody according to claim 33, in which antibody or receptorbody specifically binds the ligand of claim 14, for use in a method of blocking blood vessel growth in a mammal.

37. An antibody or receptorbody according to claim 36 for use in a method wherein the mammal is a human.

38. A ligand according to claim 34 for use in a method of promoting neovascularization in a mammal.

39. A ligand according to claim 38 for use in the promotion of wound healing.

40. A ligand according to claim 38 for use in the treatment of ischemia.

41. A TIE-2 antagonist for use in a method of inhibiting TIE-2 ligand activity in a mammal.

42. An antagonist according to claim 41 which is an antibody capable of specifically binding TIE-2 receptor.

43. An antibody according to claim 42 which is an antibody according to claim 22 or 23.

44. An antagonist according to claim 42 which is a receptorbody according to claim 22.

45. An antagonist according to claim 41 which is a ligand according to claim 15.

46. An antagonist according to any one of claims 41 to 45 for use in a method wherein the mammal is a human.

47. An antagonist according to any one of claims 41 to 46 for use in a method of attenuating or preventing tumor growth in a human.

48. A method of maintaining a TIE-2 receptor expressing cell in culture, which method comprises administering to the TIE-2 receptor expressing cell an effective amount of the ligand of claim 14.

49. A method according to claim 48 wherein the TIE-2 receptor expressing cell is an endothelial cell.

50. A method of identifying a TIE-2 receptor antagonist comprising contacting cells expressing the TIE-2 receptor with: a) a test compound; and b) a ligand according to claim 14 or 15; under conditions permitting binding of the ligand to the receptor and determining

whether the test compound is capable of interfering with the binding of the ligand to the receptor.

51. A polypeptide produced by the method of claim 19.

52. A nucleic acid according to claim 1 or 23, substantially as hereinbefore described with reference to any one of the foregoing Examples.

53. A vector according to claim 6 or 24, substantially as hereinbefore described with reference to any one of the foregoing Examples.

54. A ligand according to any one of claims 12 to 15, substantially as hereinbefore described with reference to any one of the foregoing Examples.

55. A host-vector system according to claim 16, substantially as hereinbefore described with reference to any one of the foregoing Examples.

56. A method according to claim 19, 48 or 50, substantially as hereinbefore described with reference to any one of the foregoing Examples.

57. An antibody according to claim 20 or 33, substantially as hereinbefore described.

58. A receptorbody according to claim 22 or 33, substantially as hereinbefore described with reference to any one of the foregoing Examples.

59. A conjugate according to claim 27 or 33, substantially as hereinbefore described.

60. A composition according to any one of claims 29 to 32 or 33, substantially as hereinbefore described with reference to any one of the foregoing Examples.

61. A TIE-2 antagonist according to claim 41, substantially as hereinbefore described with reference to any one of the foregoing Examples.

62. A ligandbody which specifically binds the TIE-2 receptor or the receptorbody of claim 22, 33 or 58.

63. A ligandbody which comprises a TIE-2 ligand fused to an immunoglobulin constant region.

64. The ligandbody of claim 63 wherein the TIE-2 ligand is TIE-2 ligand according to any one of claims 12 to 15 and the immunoglobulin constant region is the Fc portion of human IgG1.

65. A ligandbody according to any one of claims 62 to 64 for use in a method of treatment of the human or animal body, or in a method of diagnosis.

66. A method of treating a human or animal subject comprising administering to the subject an effective amount of a ligand according to any one of claims 12 to 15, an antibody according to claim 20 or 21, a receptorbody according to claim 22, a conjugate according to claim

27 or 28, a composition according to any one of claims 29 to 32, or a ligandbody according to any one of claims 62 to 65.

67. A method according to claim 66, the method being as defined in any one of claims 36 to 47.

68. A method according to claim 66 further comprising administering a second pharmaceutically active agent.

69. A method according to claim 68 wherein said second pharmaceutically active agent is a cytokine, neurotrophin, interleukin, cytokine antagonist, VEGF, anti-VEGF antibody, VEGF receptorbodies or bFGF.

70. A method of treating leukopenia comprising treating a patient with a therapeutically effective amount of the ligand according to claim 14.

71. A method of treating thrombocytopenia comprising treating a patient with a therapeutically effective amount of the ligand according to claim 14.

72. A method of treating anemia comprising treating a patient with a therapeutically effective amount of the ligand according to claim 14.

73. A method of enhancing bone marrow engraftment during transplantation comprising treating a patient with a therapeutically effective amount of the ligand according to claim 14.

74. A method of treating bone marrow aplasia or myelosuppression caused by radiation, chemical treatment or chemotherapy comprising

treating a patient having such aplasia or myelosuppression with a therapeutically effective amount of the ligand according to claim 14.

75. A method of treating a proliferative disorder of a blood forming organ comprising treating a patient with a therapeutically effective amount of the ligand according to claim 15, an antibody according to claim 20 or 21, a receptorbody according to claim 22, a conjugate according to claim 27 or 28, a composition according to any one of claims 29 to 32, or a ligandbody according to any one of claims 62 to 65.